

Letter to the Editor

Clarithromycin-Minocycline Combination as Salvage Therapy for Toxoplasmosis in Patients Infected with Human Immunodeficiency Virus

In December 1992, Derouin et al. (3) confirmed the efficacy and synergistic effect of the clarithromycin-minocycline combination on experimental toxoplasmosis, as previously reported by Araujo et al. (1). In this study, the survival rate of mice varied between 93 and 100% depending on the dose of each drug. Since the conventional regimens, pyrimethamine-sulfadiazine and pyrimethamine-clindamycin, are associated with a high rate of treatment-limiting adverse events (2, 4), the clarithromycin-minocycline combination was used as salvage therapy for a few patients who could not tolerate these regimens. We report this preliminary experience with the clarithromycin-minocycline combination in humans.

Eight AIDS patients were treated for toxoplasmosis with this combination, because at least two of the three main drugs caused previous treatment-limiting adverse events. They were six men and two women with a mean age of 28 to 38 years and a mean CD4 count of 18 ± 15 cells/mm³. All patients had toxoplasmosis diagnosed after suggestive contrast-enhancing lesions were found at the initial CT scan ($n = 7$), before any anti *Toxoplasma gondii* treatment was started, or after detection of *T. gondii* in broncho-alveolar lavage (patient 8). All showed a favorable response to anti-*T. gondii* therapy.

Six patients (patients 1 to 6) were assessable for acute therapy (Table 1). The combination of clarithromycin and minocycline was given as first-line therapy to two patients who had

a relapse of toxoplasmosis (patients 1 and 6) and after 17 ± 7 days of standard therapy to the four others. Clarithromycin was administered at a dose of 0.75 to 2 g/day and minocycline at a dose of 200 mg/day. The mean duration of acute therapy with the combination was 9 ± 4 weeks. During acute therapy, no other potentially active therapy for toxoplasmosis was given, except to one patient (patient 6), who was concomitantly given pyrimethamine at 75 mg/day. When the combination was started, five patients had neurological and CT scan signs of progressive cerebral toxoplasmosis and one patient (patient 4) had neurological signs and a CT scan done 2 weeks earlier that had suggested cerebral toxoplasmosis. Two patients (patients 1 and 2) with partial neurological and CT scan responses died at weeks 8 and 12, of causes unrelated to toxoplasmosis: human immunodeficiency virus encephalitis for one, and shock related to *Clostridium difficile* colitis for the other. The four other patients had complete clinical resolution, with minimal radiological sequelae in three and complete CT scan response in one. However, in three of them, the presumed benefit of clarithromycin-minocycline could be due to the earlier standard therapy. The clarithromycin-minocycline combination had to be discontinued only once (patient 2), due to a fivefold increase in serum transaminase levels in a patient who had concomitant potentially hepatotoxic drugs for tuberculosis.

Maintenance therapy was assessed for six patients (patients

TABLE 1. Characteristics of patients treated for toxoplasmosis with the clarithromycin-minocycline combination

Patient no. (sex, CD4 cells/mm ³)	Previous standard Rx or duration of acute Rx ^a	Assessment for Rx		Clinical sign(s) ^b	CT scan lesion(s) ^b (site)	Acute Rx		Response to maintenance Rx (final outcome, time of assess- ment ^c)
		Acute	Maintenance			Clinical response (duration of acute Rx ^c)	CT scan response (time of assessment ^c)	
1 (M, 23)	None	Yes	No	Fever, headache, hemi- plegia	Multiple (cerebral)	Partial ^d (8 wk)	Partial ^d (day 25)	NA ^e (death, wk 8)
2 (M, 7)	1 wk	Yes	No	Headache, confusion, hemiplegia	Multiple (cerebral)	Partial ^d (12 wk)	Partial ^d (day 21)	NA (death, wk 12)
3 (F, 12)	2 wk	Yes	Yes	Cerebellar syndrome	Unique (cerebral)	Complete (3 wk)	Complete (day 20)	No relapse ^f (alive, 7 months)
4 (F, 20)	2 wk	Yes	Yes	Confusion, cerebellar syndrome	ND ^g (cerebral)	Complete (10 wk)	Partial ^d (day 71)	No relapse (death, 7.5 months)
5 (M, 3)	3 wk	Yes	Yes	Cerebellar syndrome	Multiple (cerebral)	Complete (8 wk)	Partial ^d (day 58)	No relapse (alive, 7.5 months)
6 (M, 17)	None	Yes	Yes	Fever, headache	Multiple (cerebral)	Complete (12 wk)	Partial ^d (day 60)	Relapse ^{f,h} (alive, 12 months)
7 (M, 8)	2 wk	No	Yes	None	None (cerebral)	NA	NA	No relapse ^f (alive, 3 months)
8 (M, 21)	7 wk	No	Yes	None, normal chest X ray	NA (pulmonary)	NA	NA	No relapse (alive, 4.5 months)

^a Rx, therapy.

^b At the time the clarithromycin-minocycline combination was initiated.

^c After initiation of clarithromycin-minocycline.

^d Greater than 50% reduction in neurological manifestations or size of lesions on CT scan.

^e NA, not assessed.

^f Concomitant co-trimoxazole for *Pneumocystis carinii* prophylaxis.

^g ND, not done. A CT scan had been done for this patient at the start of standard treatment (2 weeks before the start of the treatment with clarithromycin-minocycline), and it showed multiple contrast-enhancing cerebral lesions.

^h Relapse at 12 months (only CT scan impairment).

3 to 8) who had complete clinical responses and complete (patients 3, 7, and 8) or partial (patients 4, 5, and 6) radiological responses after 3 to 9 weeks of acute therapy with the clarithromycin-minocycline combination (four patients) or conventional regimens (two). Clarithromycin was used at a dose of 1 to 1.5 g/day, and minocycline was used at a dose of 100 to 200 mg/day. Co-trimoxazole (one single-strength tablet per day) was also given to three patients. Mean follow-up was 7 months (patients 3 to 12). Relapse occurred after 12 months in one noncompliant patient (patient 6) who was taking concomitant co-trimoxazole, but in none of the other five patients. One patient (patient 4) died after 7.5 months after neurological manifestations attributed to a stroke. No treatment-limiting adverse event was recorded.

In this preliminary experience, the clarithromycin-minocycline combination, used as salvage therapy for toxoplasmosis, allowed us to complete or achieve acute therapy in AIDS patients with previous adverse events to conventional regimens. This combination seems capable of limiting the risk of relapse when used as secondary prophylaxis. The rate of treatment-limiting adverse events related to this combination appears to be moderate. These data support the favorable results reported for the murine model (1, 3). They warrant further studies to assess this combination along with other alternative regimens, such as atovaquone (5), which might benefit the patients unable to tolerate conventional therapies.

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